Am J Hum Genet 39:648–660, 1986

Paternal Age and the Occurrence of Birth Defects

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SUMMARY

The association between paternal age and the occurrence of birth defects was studied using data collected in Metropolitan Atlanta. Paternal-age information for babies born with defects was obtained from birth certificates, hospital records, and interviews with mothers; for babies born without defects, the information was obtained from birth certificates. Several statistical techniques were used to evaluate the paternal-age-birth-defects associations for 86 groups of defects. Logistic regression analysis that controlled for maternal age and race indicated that older fathers had a somewhat higher risk for having babies with defects, when all types of defects were combined; an equivalent association for older mothers was not found. Logistic regression analyses also indicated modestly higher risks for older fathers for having babies with ventricular septal defects and atrial septal defects and substantially higher risks for having babies with defects classified in the category chondrodystrophy (largely sporadic achondroplasia) and babies with situs inversus. An association between elevated paternal age and situs inversus has not been reported before; the magnitude of the estimated increased risk for situs inversus was about the same as that found in this study for chondrodystrophy.

INTRODUCTION

Most research into the causes of human birth defects has been directed at factors that act through the mother, either before or after conception. This focus may have been prompted by the well-established associations between

Received July 12, 1985; revised March 3, 1986.

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 0002-9297/86/3905-0010$02.00

birth defects and maternal drug exposures (e.g., thalidomide) and infections (e.g., rubella). Moreover, most experimental work with animals has dealt with mother/embryo exposures or mechanisms, and what little work has been done with paternal exposures does not suggest that they are major contributors to the occurrence of malformed offspring.

Some paternal associations in humans have been found, however. In 1955, Penrose [1] demonstrated that the statistical association between parental ages and birth order and defects caused by fresh dominant mutations is largely attributable to the age of the father, not to mother's age or birth order [1]. More recently, it has been shown that Down syndrome can occur because of paternal nondisjunction [e.g., 2–4], despite the long-standing research focus on maternal factors. This cytogenetic evidence has generated a number of studies that have renewed a long abandoned search for a paternal-age association with Down syndrome [e.g., 5–7]. With some exceptions, these studies have not demonstrated an association, and if paternal age does affect the occurrence of Down syndrome, the effect must be much smaller than the maternal-age effect [6].

Recent interest in the possibility of paternal contributions to the occurrence of birth defects has also been prompted, at least in Australia and the United States, by the concerns of Vietnam veterans that they have been at increased risk of fathering babies with birth defects, allegedly due to their exposure to the dioxin-containing herbicide known as Agent Orange [8].

The conduct of a study designed to determine if U.S. Vietnam veterans have been at such increased risk ([8]; hereafter this study will be referred to in this paper as the "VV Study") provided the opportunity to gather a wide variety of information about fathers who have had babies with birth defects, including information on their ages at the time of their babies' births. This has made possible the comprehensive search for paternal-age/birth-defects associations described in this report.

DATA AND METHODS

Birth Defects Information

Since 1968 the Metropolitan Atlanta Congenital Defects Program (MACDP) has registered babies with structural congenital malformations born to mothers who were residents of the five-county area surrounding and including the city of Atlanta. This program ascertains these babies through an active and aggressive surveillance program that makes use of multiple sources of information, including regular visits to area hospitals by program staff [9]. Of approximately 13,000 stillborn and live-born babies with birth defects registered by the MACDP in 1968–1980, 7,530 who were born with defects defined as "major" or "serious" were selected for the VV Study [8]. About 400 babies with these types of malformations were excluded from that study. Most of the reasons for exclusion were of no relevance to the present study, and only 40 were excluded here. Some of the 40 exclusions were made because of registration errors discovered in the course of the VV Study. In addition, for the present study, one member of each defect-concordant twin pair was excluded. The final number eligible for this study was 7,490 (these babies are hereafter referred to as "cases").

In the routine operation of the MACDP, the descriptions of the defects that occurred in the registered babies have been abstracted from hospital charts onto MACDP case

record forms and later coded according to a special modification of the 8th Revision of the International Classification of Disease ("ICD-8").

These defects were arranged into 86 groups for analysis, based on the modified ICD-8 code (table 1); if a baby had two or more defects, he or she was counted in each relevant defect group.

Age of Parents and Race

Paternal and maternal ages were obtained from the records described below. The ages were accepted as valid if they were from 13 through 71 years for fathers and from 12 through 49 years for mothers.

(1) *For babies born with defects ("cases").* Three potential sources of parental-age information were available: (a) MACDP case record forms (available for all cases), (b) State of Georgia certificates of live birth (available for a majority of live-born cases), and (c) special interviews, which were conducted during the years 1970–1979 with the

TABLE 1

NOS. BABIES BY TYPE OF DEFECT AND KNOWN AND UNKNOWN PATERNAL AGE, MATERNAL AGE, AND RACE

DEFECT GROUP		PATERNAL AGE, MATERNAL AGE, AND RACE		
Code*	Description	Known	Unknown	Total
...	All defects	6,384	1,106	7,490
...	Total neural tube defects	471	77	548
7400	Anencephalus	186	53	239
...	Total spina bifida	285	24	309
7410	Spina bifida with hydrocephalus	168	14	182
7419	Spina bifida without hydrocephalus	117	10	127
7420	Hydrocephalus	239	109	348
7430	Encephalocele	59	5	64
7431	Microcephalus	104	39	143
7434	Neurofibromatosis	7	0	7
7440	Anophthalmos	20	6	26
7441	Microphthalmos	67	16	83
7442	Buphthalmos	11	4	15
7443	Congenital cataract	55	19	74
7444	Coloboma	23	3	26
7445	Aniridia	6	0	6
7450	Anomalies of ear causing hearing impairment	38	10	48
7460	Common truncus	23	7	30
7461	Transposition of great vessels	117	10	127
7462	Tetralogy of fallot	83	9	92
7463	Ventricular septal defect	532	123	655
7464	Atrial septal defect	222	56	278
7465	Ostium atrioventriculare commune	54	6	60
7466	Anomalies of heart valves	203	30	233
7467	Fibroelastosis cordis	14	0	14
7470	Patent ductus arteriosus	486	128	614
7471	Coarctation of aorta	98	13	111
7472	Other anomalies of aorta	88	12	100
7473	Stenosis or atresia of pulmonary artery	105	21	126
7474	Anomalies of great veins	54	7	61
7480	Choanal atresia	28	5	33
7484	Congenital cystic lung	5	4	9
7485	Agenesis of lung	10	2	12
7490	Cleft palate	183	20	203
...	Cleft lip with/without cleft palate	326	26	352

Table 1 continued on next page

TABLE 1 (continued)

Defect group		Paternal age, maternal age, and race		
Code*	Description	Known	Unknown	Total
7491	Cleft lip	108	8	116
7492	Cleft palate and cleft lip	218	18	236
7501	Pyloric stenosis	428	24	452
7502	Tracheo-esophageal fistula, esophageal atresia and stenosis	72	2	74
7511	Atresia and stenosis of small intestine	98	5	103
7512	Atresia and stenosis of rectum and anal canal	129	13	142
7513	Hirschsprung disease	43	9	52
7514	Anomalies of intestinal fixation	67	7	74
7516	Anomalies of gall-bladder, bile ducts, and liver	92	25	117
7517	Anomalies of pancreas	9	1	10
7520	Indeterminate sex	5	1	6
7522	Hypospadias	730	118	848
7523	Epispadias	20	8	28
7525	Anomalies of ovary, fallopian tube, and uterus	23	9	32
7526	Anomalies of vagina and external female genitalia	58	15	73
7527	Pseudohermaphroditism	34	10	44
7530	Renal agenesis	80	10	90
7531	Cystic kidney disease	67	15	82
7532	Obstructive defects of urinary tract	118	28	146
7535	Exstrophy of urinary bladder	15	1	16
7536	Atresia and stenosis of urethra and bladder neck	68	12	80
7540	Clubfoot	1,132	177	1,309
...	Total limb reduction deformity	225	28	253
7552	Reduction deformity of upper limb	163	20	183
7553	Reduction deformity of lower limb	62	7	69
7554	Reduction deformity, unspecified limb	0	1	1
7558	Generalized flexion contracture	39	6	45
7564	Chondrodystrophy	21	5	26
7565	Osteogenesis imperfecta	12	2	14
7570	Hereditary edema of legs	4	0	4
7573	Specified anomalies of hair	14	5	19
7574	Specified anomalies of nails	31	9	40
7580	Anomalies of spleen	51	17	68
7581	Anomalies of adrenal gland	7	4	11
7582	Anomalies of thyroid gland	29	4	33
7583	Anomalies of other adrenal glands	14	7	21
7590	Situs inversus	18	5	23
7591	Conjoined twins	8	1	9
7592	Other form of monster	5	1	6
...	Autosomal chromosome defects	346	40	386
7593	Down syndrome	290	28	318
7594	Other syndromes due to autosomal abnormality	56	12	68
7596	Tuberous sclerosis	2	0	2
7598	Other specified syndromes	114	40	154
7599	Multiple congenital anomalies, unspecified	4	3	7
S603	Diaphragmatic hernia	94	13	107
S606	Omphalocele and gastroschisis	143	20	163
S621	Other neoplasm	111	13	124
S702	Cytomegalovirus	14	5	19
S704	Herpes simplex	9	3	12
S705	Syphilis	17	18	35

* Code numbers are modified from International Classification of Disease, 8th Revision. Defect groups without code numbers are combinations of other defect groups.

mothers of babies born with selected defects (available for about 1,200 live-born and stillborn cases; the information collected during the interviews done for the VV Study was not used in the present study—that interviewing was completed after the data for the present study were assembled).

Mother's age was almost always recorded on the MACDP case record, and therefore the record was the source of maternal age for almost all cases. Even though an MACDP case record was available for each case baby, and a live-birth certificate was not, the certificate was the preferred source of father's age because the age was more frequently recorded on the certificate than on the case record. In those instances where the father's age could not be obtained from the certificate, the MACDP case records and the special interviews were checked for the presence of father's age. If the age was found in one of these supplemental sources, it was used in the analysis; if the age was present in both supplemental sources, it was taken from the interview. The use of case records and interviews to supplement the information derived from birth certificates was considered reasonable for the following reasons: (a) birth certificates could be obtained only for live-born case babies, and the case records and/or interviews provided the only source of information for stillborn case babies, and (b) in those instances where paternal ages were available from the birth certificates and from the case records and/or from the interviews, there was close agreement between the ages recorded (95% plus or minus 1 year). Information about the race of case babies was obtained from the MACDP case records.

(2) *For babies born without defects ("controls").* Information about the ages of the parents of, and the race of, 333,624 babies live born 1968–1980 to mothers resident in the five-county MACDP surveillance area was sought from the State of Georgia Vital Records Unit's magnetic tape of coded birth certificates.

Statistical Methods

The statistical analysis, designed to search for paternal-age associations within each of the 86 defect categories, had three parts:

(1) Cases and controls were stratified by father's age (eight groups: < 20, 20–24, 25–29, and so on, to the upper group of 50 years and over). A 7 d.f. chi-square test for independence and a 1 d.f. extended Mantel-Haenszel chi-square test for a linear trend in proportions were performed [10].

(2) Cases and controls were stratified by maternal age (seven groups: < 20, 20–24, 25–29, . . . 45–49 years) and by race (white and other) and assessed for evidence of paternal-age associations in the following way:

(a) The case and control data were divided into two groups, one group with fathers' ages 30 years and over ("old" fathers) and the other group with fathers' ages under 30 ("young" fathers). A Mantel-Haenszel summary chi-square and summary odds ratio (M-H OR) were then computed [10]. The M-H OR estimates the risk of having a baby with a defect for fathers 30 years and over, relative to the risk for fathers under 30, adjusted for maternal age and race.

(b) This process was repeated four other times, with the following groupings of fathers' age: 35 years and over vs. under 35, 40 years and over vs. under 40, 45 years and over vs. under 45, and 50 years and over vs. under 50.

These tests thus compared the risk for older fathers with the risk for younger fathers, using five different definitions of "old" and "young." This approach is a large sample approximation to the method proposed by Stene and Stene [11] and is most sensitive to a relatively sharp change in paternal-age-specific rates at some particular age. An example of this type of age association would be that between Down syndrome and maternal age.

(3) Logistic regression [10, 12] was the third analytical approach used; computations were made using the Statistical Analysis System [13] PROC FUNCAT. The regressions were used to relate paternal and maternal age (single years of age) and race (white, other) to whether a member of the study sample had a birth defect (d = 1) or not (d = 0).

Denote the independent regression variables (parental ages and race) as the vector

$\underline{x} = (x_1, x_2, x_3)$. By the logistic model,

$$P(\underline{x}) = \text{pr}(d = 1|\underline{x}) = \frac{\exp\left(\alpha + \sum_{k=1}^{3} B_k x_k\right)}{1 + \exp\left(\alpha + \sum_{k=1}^{3} B_k x_k\right)}$$

or

$$\ln \frac{P(\underline{x})}{1 - P(\underline{x})} = \text{logit}[\text{pr}(d = 1|\underline{x})] = \alpha + \sum_{k=1}^{3} B_k x_k .$$

This implies that the ratio of the odds for the presence of a defect (odds ratio), given two different sets of regression variables, $\underline{x}^*$ and $\underline{x}$, is

$$\exp\left\{ \sum_{k=1}^{3} B_k(x^* - x) \right\} .$$

Thus, $EXP(B_k)$ is the fraction by which the risk is changed for a unit change in x_k [12]. In this paper, the quantity $EXP(B_k)$ will be described as a "logistic regression odds ratio." Since paternal age was entered in the model by single years of age, the logistic regression odds ratio for paternal-age estimates the change in risk for a change of 1 year in paternal age. Because maternal age and race were included in the regressions, the logistic regression odds ratios presented for paternal age can be considered as being "adjusted" for maternal age and race. Ancillary race-specific logistic regressions were also done; that is, regressions including only paternal and maternal age as independent variables were done separately for whites and for other races. These analyses were done to check for the possibility that the birth defect-paternal age associations differed between the two race groups.

Associations between paternal age, maternal age, or race and a specific defect category or group of defects with significance probabilities less than or equal to .05 are considered statistically significant. The probability values correspond to the Wald chi-square statistics given by PROC FUNCAT [13].

RESULTS

Parental Age and Race Data

Of the 7,490 total case babies, 6,384 (85.2%) had known paternal and maternal ages and race (table 1). The remainder (1,106) had to be excluded from this study; almost all had to be excluded because of unknown paternal age—one case baby was of unknown race, and 10 had unknown mother's and father's ages. About 90% of the paternal ages for cases in this study came from birth certificates, 5% from interviews, and 5% from case record forms.

From among the 333,624 total live-born babies, about 87% had known paternal and maternal ages and known race. Because these babies include the live-born case babies with known parental ages and race, a record was deleted from the file for each live-born case baby included in this study. This deletion was made on the basis of the ages of the baby's parents and the baby's race. The final number of control babies available for this study was 284,497.

Paternal-Age Associations

The results of the statistical analyses are presented in table 2; only those defect groups that meet the following criteria are shown: (1) 15 or more cases

TABLE 2

ASSOCIATION OF PATERNAL AGE AND BIRTH DEFECTS

CODE	DEFECT DESCRIPTION	No. CASES	CHI-SQUARE†		RISK AT AND ABOVE SPECIFIED PATERNAL AGE RELATIVE TO RISK BELOW AGE, ADJUSTED FOR MATERNAL AGE AND RACE*					LOGISTIC REGRESSION ODDS RATIO‡	
					PATERNAL AGE						
			Ind	M-H	30	35	40	45	50		
...	All case babies	6,384	28.242	17.228	1.04	1.02	1.20	1.17	1.26	1.01	W
7400	Anencephalus	186	5.236	2.193	0.88	0.57	0.54	1.23	1.31	0.97	W
7420	Hydrocephalus	239	10.056	2.214	1.08	1.13	1.92	1.18	1.44	1.03	
7440	Anophthalmos	20	8.084	2.520	0.67	0.00	0.00	0.00	0.00	0.89	
7441	Microphthalmos	67	12.283	4.127	1.38	1.08	1.57	3.52	2.45	1.05	
7444	Coloboma	23	10.341	0.646	1.12	0.90	0.92	4.36	14.82	1.06	W
7461	Transposition of great vessels	117	9.056	1.927	0.83	1.19	2.07	3.63	3.88	1.00	
7463	Ventricular septal defect	532	12.058	8.308	1.19	1.27	1.69	1.41	1.03	1.03	
7464	Atrial septal defect	222	18.766	11.962	1.24	1.95	1.49	1.08	0.63	1.03	
7465	Ostium atrioventriculare commune	54	14.435	2.871	0.97	0.76	1.40	1.01	0.00	0.97	AO
7466	Anomalies of heart valves	203	15.023	9.893	1.33	1.38	1.14	0.51	0.00	1.02	
7470	Patent ductus arteriosus	486	4.835	4.035	1.10	1.08	1.06	0.91	0.79	1.00	AO
7473	Stenosis or atresia of pulmonary artery	105	18.702	0.033	0.85	1.37	1.68	4.88	4.20	1.02	
7492	Cleft palate and cleft lip	218	11.828	0.006	0.76	1.07	1.41	2.86	1.16	1.00	W

7501	Pyloric stenosis	428	14.091	2.317	0.91	1.12	1.08	1.65	1.09	1.01	W
7502	Tracheo-esophageal fistula, esophageal atresia, and stenosis	72	4.587	3.290	1.10	1.05	1.26	0.00	0.00	1.00	W
7513	Hirschsprung disease	43	5.881	3.395	1.66	1.99	1.54	2.37	0.00	1.05	
7523	Epispadias	20	9.840	1.505	1.48	0.35	1.00	0.00	0.00	0.98	
7527	Pseudohermaphroditism	34	10.465	0.271	1.23	0.57	2.12	9.23	9.47	1.01	
7530	Renal agenesis	80	14.172	1.640	0.40	0.90	0.88	3.93	0.00	0.98	
7535	Exstrophy of urinary bladder	15	6.490	4.426	1.48	0.00	0.00	0.00	0.00	0.93	
7540	Clubfoot	1,132	11.000	3.713	1.02	0.93	1.11	0.45	0.45	1.00	YW
7552	Reduction deformity of upper limb	163	10.514	0.336	0.75	1.02	0.75	1.22	1.50	0.99	
7558	Generalized flexion contracture	39	10.360	4.028	1.54	1.99	0.50	0.83	0.00	1.03	
7564	Chondrodystrophy	21	60.988	11.255	10.08	2.75	13.32	0.00	0.00	1.12	
7574	Specified anomalies of nails	31	10.897	0.148	1.25	1.83	2.43	4.47	6.51	1.02	O
7580	Anomalies of spleen	51	19.200	1.504	0.39	1.09	2.42	1.68	1.39	1.01	O
7590	Situs inversus	18	62.762	5.629	2.30	4.46	19.27	5.91	11.12	1.13	O
...	Autosomal chromosome defects	346	146.236	79.273	1.06	1.02	1.29	1.20	1.61	1.01	AO
7593	Down syndrome	290	141.001	82.026	1.07	1.01	1.21	1.25	1.65	1.01	A
7594	Other syndromes due to autosomal abnormality	56	18.134	2.329	0.96	1.10	2.02	0.92	1.38	1.01	
7598	Other specified syndromes	114	6.133	1.856	0.92	0.84	0.92	1.11	2.28	0.99	O
S603	Diaphragmatic hernia	94	18.205	0.813	0.96	0.71	1.08	1.36	5.26	1.01	
S606	Omphalocele and gastroschisis	143	7.833	2.625	0.95	1.34	1.33	0.37	0.00	1.01	Y

* Mantel-Haenszel odds ratio estimates of relative risk; odds ratios with associated P values $< .05$ are underlined.

† Chi-square values. Ind = χ^2 for independence, 7 df; $P = .20$, 9.803. M-H = Mantel-Haenszel χ^2 for linear trend in proportions, 1 df, $P = .20$, 1.642.

‡ Logistic regression odds ratio, see text for explanation; odds ratios with associated P values $< .05$ are underlined; defects with significant ($P < .05$) maternal-age effect marked "Y" for higher rates for younger ages, "A" for advanced ages; defects with significant race effect marked "W" for higher rates for whites, "O" for other races.

with known parental ages and race, and (2) for the first two paternal-age tests, a probability value of less than .20 for the independence chi-square and/or the extended Mantel-Haenszel chi-square for linear trend in proportions. For each of these defect groups, table 2 has the two probability values just mentioned, the M-H OR for the analyses based on the five groupings of paternal age into "old" and "young" (these analyses were adjusted for maternal age and race) and the logistic regression OR for paternal age, adjusted for maternal age and race. Statistically significant ORs are underlined; statistically significant maternal age or race associations by logistic regression are also noted.

When all case babies were combined into one group, elevated paternal age was weakly but statistically significantly associated with the occurrence of defects (logistic regression OR = 1.01, table 2). The race-specific regressions (results not shown in table) found a significant logistic regression OR for whites but not for other races, although the OR for other races was greater than 1.0. There was no similar association between maternal age and overall defect occurrence, although there was a statistically significant race effect, whites having a higher rate of defects than other races (table 2). Fathers 40 years of age and over had a (statistically significant) 20% greater risk (M-H OR = 1.20) of having a baby with a birth defect compared to fathers under 40. The remainder of the "old" vs. "young" father comparisons did not yield significant probabilities, but the OR for the comparisons where the definitions of "old" were 45 years and older and 50 years and older also indicated greater risks of about 20% (table 2).

Weak and positive associations were found by the logistic regression analyses between paternal age and both ventricular septal defect (VSD) and atrial septal defect (ASD) (table 2). For VSD, the comparison of the risk for fathers 40 years and over relative to those under 40 gave a significant M-H OR of 1.69, and for ASD the comparison of the risk for fathers 35 years and over vs. fathers under 35 gave a significant OR of 1.95.

The most striking findings of this study were for chondrodystrophy and situs inversus (table 2). The chondrodystrophy result was expected, based on the available literature, but the result for situs inversus was not. The logistic regression ORs for these two defect groups were about the same. The logistic regression ORs obtained when paternal age, maternal age, and race were included as independent variables were 1.12 and 1.13 for chondrodystrophy and situs inversus, respectively (table 2). The race-specific regressions gave ORs for chondrodystrophy of 1.14 for whites ($P < .05$) and 1.09 for other races ($P > .05$); for situs inversus, the OR for whites was 1.18 ($P < .05$) and for other races it was 1.10 ($P < .05$). Despite the similarity of the logistic regression results, the pattern of the results of the Mantel-Haenszel comparisons of "old" vs. "young" fathers differed. For chondrodystrophy, fathers 30 years of age and over were 10 times as likely to have a child with chondrodystrophy as fathers under 30 years of age. Fathers 40 years and over had a relative risk of 13 (table 2). No fathers of babies with chondrodystrophy were 45 years of age or older, and the computed relative risks were therefore 0.0 for older fathers, when older was defined as 45 years and over and 50 years and over.

All analyses for the defect category "chondrodystrophy" were repeated after deleting four cases whose defect might not be due to a fresh mutation because either one or both parents were affected with a chondrodystrophy (according to information on the MACDP case records) or because the chondrodystrophy might have been due to a recessive gene. These reanalyses somewhat reduced the "old" vs. "young" test M-H ORs presented in table 2 and made the logistic regression OR for paternal age no longer statistically significant (OR = 1.08, P = .07).

For situs inversus, the comparison of fathers 30 years and over to fathers under 30 did not yield a significant M-H OR, but all of the remaining tests of "old" vs. "young" fathers gave statistically significant relative risks. Since seven of the babies with situs inversus also had an ASD, the analyses for ASD were repeated, excluding those who had situs inversus. The statistically significant logistic regression OR of 1.03 persisted.

For the analyses that did not take account of maternal age (chi-squares for independence and extended Mantel-Haenszel for trend in proportions), paternal age was very strongly associated with Down syndrome and other anomalies of the autosomal chromosomes (table 2). However, this apparent paternal-age effect disappeared in the logistic regression analyses that adjusted for maternal age by single years of age.

DISCUSSION

This study confirms the previously described association between elevated father's age and increasing risks of fathering babies with defects classified in the category "chondrodystrophy." This category largely comprises babies with achondroplasia, most of whom presumably were affected because of a fresh dominant mutation. The underlying paternal-age association must be quite strong, being detectable even with the small number of cases (no. 21) available for this study. A similarly striking association was seen for the category situs inversus. If this association is not simply a chance event, perhaps the association indicates that some cases result from fresh dominant mutation; to our knowledge, no such dominant phenotype has been recognized [14].

Unlike the situation with achondroplasia and other syndromes due to dominant mutations, we are unaware of any other study of statistical associations between paternal age and situs inversus. Indeed, other than for the dominant phenotypes [15], little work has been done on paternal-age associations, and our present study is probably unique in the comprehensiveness of its search. Although Gittelsohn and Milham [16] made a comprehensive search for paternal-age effects, they ascertained defects for that study from birth certificates, generally known to be an incomplete source with rather poor diagnostic specificity. Polednak [17] made a similar analyses of later data from the same source. Two of the strengths of our present study are that the ascertainment for the MACDP is made through the use of multiple information sources and that ascertainment is done through the first year of life. This gives a much more comprehensive ascertainment of some defects, such as those of the heart, which are often not recognized by the time the birth certificate is filled out; that

is not to say, however, that the ascertainment of such defects by the MACDP is necessarily complete. In addition, the thorough review made of the hospital charts of all case babies by the MACDP staff gives better diagnostic specificity than that available from birth certificates; even better diagnostic specificity would be obtained, of course, if there had been examinations of babies made specifically for the MACDP.

A potential weakness of this study is that about 15% of cases and controls had to be excluded, primarily because paternal age was not recorded on the available records. Father's age was most often missing from the records of babies of young, unmarried mothers. Because maternal and paternal age are positively correlated, most excluded fathers would have been young. Since the correlation is not perfect, and because fathers generally tend to be older than their mates, some of the fathers excluded would have been substantially older than their mates. A preferential exclusion of babies with fathers substantially older than mothers will have reduced the power of this study to detect a paternal-age effect, particularly for any defect with a strong maternal-age effect. But since only about 15% of cases and controls had to be excluded, this reduction in power should not be too great.

Because maternal age is strongly correlated with paternal age, it seemed reasonable that some of our analyses for each defect group should include an adjustment for maternal age so that a paternal-age effect could be evaluated free of the confounding effects of maternal age. Race is also related to the occurrence of some defects, and it is associated with parental age; it is thus a potential confounder of any paternal-age relationships. Because of this, some of the analyses performed included adjustments for race. It is also possible that a paternal-age association might vary with race. To evaluate this possibility, race-specific logistic regression analyses were done. Although it is conceivable that there are other factors that might confound, or interact in, the relationship between paternal age and defect occurrence, we were not able to explore this issue in this study.

Recently, the discovery that Down syndrome can result from paternal nondisjunction [2, 3] has raised considerable interest in the possibility that paternal age might be associated with Down syndrome. The data presented here on Down syndrome were largely presented before [6]. These data show a marked crude paternal-age association, an association that disappears once account is taken of maternal age. In other words, the marked crude paternal-age association appears to be largely secondary to the well-documented maternal-age association and the high correlation between maternal and paternal age. In general, this has been the finding in other studies, although some authors have found some relatively weak evidence of a paternal-age effect [5, 18, 19].

What statistical methods should be used for detecting paternal-age effects is controversial, particularly in instances where a maternal-age effect is concomitantly strong, as in Down syndrome [6, 11, 20]. Briefly, the issue devolves to whether control for a maternal-age effect should involve single years of maternal age or whether groupings of age (e.g., by 5-year age intervals) are sufficient. Those who have made adjustment by single years of age generally have found no evidence of a paternal-age effect for Down syndrome, whereas those who

have used coarser groupings have. If a fine adjustment for a strong maternal-age effect is not done, then at least a part of the apparent paternal-age effect will be the result of the maternal-age effect [6, 20]. On the other hand, the argument in favor of the use of coarse maternal-age groupings involves the notion that the adjustment for single years of maternal age will reduce statistical power [21]. Although we favor the former approach for those defect categories with strong maternal-age effects, most defects studied here are not strongly associated with maternal age, and we have therefore made use of several analytic approaches in this study.

The finding of some relatively weak paternal-age associations with several categories of heart defects is of interest. These categories are composed of defects that surely must be heterogeneous with respect to cause. Perhaps the weak statistical associations found in this study are the result of some of these defects being due to unrecognized dominant mutations. A few recognized syndromes due to dominant mutations have heart defects as a feature—for example, the Holt-Oram syndrome [14].

For all types of defects combined, elevated paternal age was significantly associated with an increased risk of having babies with the defects included in this study according to the logistic regression analysis, whereas maternal age was not. In these regressions, the parental-age effects are adjusted for each other. There is a significant paternal-age effect when maternal age is "held constant," but no maternal age effect when paternal age is "held constant." It is worth mentioning, however, that a logistic regression analysis of the maternal-age effect done without consideration of paternal age gave a significant maternal-age effect. Also, it must be kept in mind that this study did not include all types of defects, only those defined as "major" or "serious."

Friedman [15] estimated the risk for fathers 40 years of age and over for having babies with defects caused by fresh dominant mutations. On a number of assumptions, he speculates that this risk is "no less than" three to five per 1,000 births, which is of the same order as the risk of Down syndrome for mothers about 35 years of age. Because of this latter risk, pregnant women who are 35 years of age or older are often counseled regarding the availability of prenatal diagnosis through amniocentesis. As a risk-based recommendation, Friedman [15] suggests that men should complete their families before age 40.

The logistic regression OR for all defects combined (1.01) implies a risk of 1.2 for a father of 40 years of age relative to a very young father of, say, 20 years of age ($1.2 = 1.01^{[40-20]}$); for an age of 50 the implied relative risk is about 1.3. If one assumes that the absolute risk for having a baby with a serious defect for a father of 20 years of age is 20 per 1,000 births, then the absolute risk implied for a father of age 40 would be 24 per 1,000 births, and for a father of age 50, 26 per 1,000. This excess of four to six per 1,000 is very close to the estimate of Friedman [15] for the absolute risk for having a baby with a defect due to dominant mutation for fathers 40 and over. Friedman considers his estimate to be conservative, or minimum; Hook [22], on the other hand, believes that Friedman's estimate is likely to be liberal rather than conservative. In any case, it is possible that the similarity between Friedman's estimate and the results of the present study is coincidental. This study entertains the possibility of a

different risk for older fathers due to any mechanism, not just dominant mutations. Furthermore, it is conceivable that our present study may include defects for which younger fathers are at increased risk. Even so, the results of this study suggest that elevated paternal age might be added to the array of factors that prospective parents consider when planning their families.

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